

AMENDMENTS TO THE CLAIMS

1-37. (Canceled)

38. (Currently Amended) A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal, in a single daily oral dosage, a composition including one or more di-, tri- or tetra-peptidyl boronate or di-, tri- or tetra-peptidomimetic boronate protease inhibitors, wherein the boronate replaces the C-terminal carboxylate moiety, which inhibit DPIV-mediated proteolysis with a K_i of less than about 10 nM in an amount sufficient to modify glucose metabolism but not sufficient to suppress the immune system of the animal.

39. (Currently Amended) A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal, in a single daily oral dosage, a composition including one or more di-, tri- or tetra-peptidyl boronate or di-, tri- or tetra-peptidomimetic boronate protease inhibitors, wherein the boronate replaces the C-terminal carboxylate moiety, which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) with a K_i of less than about 10 nM in an amount sufficient to modify glucose metabolism but not sufficient to suppress the immune system of the animal.

40. (Currently Amended) A method for modifying metabolism of a peptide hormone in a glucose intolerant animal, comprising administering to the animal a composition, in a single daily oral dosage, including one or more di-, tri- or tetra-peptidyl boronate or di-, tri- or tetra-peptidomimetic boronate inhibitors of dipeptidylpeptidase IV (DPIV), wherein the boronate replaces the C-terminal carboxylate moiety and wherein the inhibitor inhibits DPIV with a K_i of less than about 10 nM, in an amount sufficient to increase the plasma half-life of the peptide hormone, which peptide hormone is selected from glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y, wherein the composition is administered in an amount sufficient to modify the metabolism of the peptide hormone but not sufficient to suppress the immune system of the animal.

41. (Previously Presented) A method for modifying glucose metabolism of a glucose intolerant animal, comprising administering to the animal a composition including a boronyl peptidomimetic inhibitor of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala in an amount sufficient to modify glucose metabolism but not sufficient to suppress the immune system of the animal.

42-45. (Canceled)

46. (Previously Presented) The method of any one of claims 38, 39, 40, or 41, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

47. (Previously Presented) The method of any one of claims 38, 39, 40, or 41, wherein the inhibitor has an EC₅₀ for modification of glucose metabolism which is at least one order of magnitude less than its EC₅₀ for immunosuppression.

48. (Previously Presented) The method of any one of claims 38, 39, 40, or 41, wherein the inhibitor has an EC₅₀ for inhibition of glucose tolerance in the nanomolar or less range.

49. (Previously Presented) The method of any one of claims 38, 39, 40, or 41, wherein the inhibitor has an EC₅₀ for immunosuppression in the μ M or greater range.

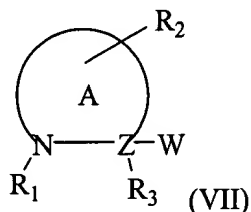
50. (Previously Presented) The method of any one of claims 38, 39, 40, or 41, wherein the inhibitor has a K_i for DPIV inhibition of 0.5 nM or less.

51. (Previously Presented) The method of any one of claims 38, 39, or 40, wherein the inhibitor is peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

52. (Previously Presented) The method of any one of claims 38, 39, 40 or 41, wherein the inhibitor has a molecular weight of less than 7500 amu.

53. (Previously Presented) The method of claim 41, wherein the inhibitor is administered orally.

54. (Currently Amended) The method of any one of claims 38, 39, 40, or 41, wherein the inhibitor is represented by the general Formula VII:

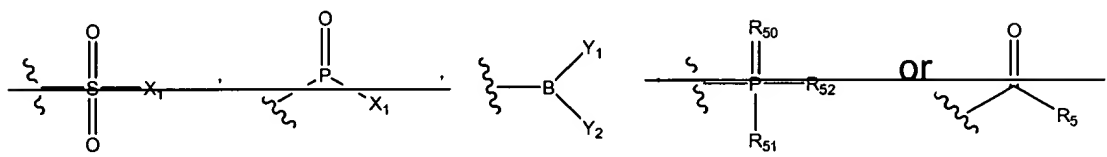


wherein,

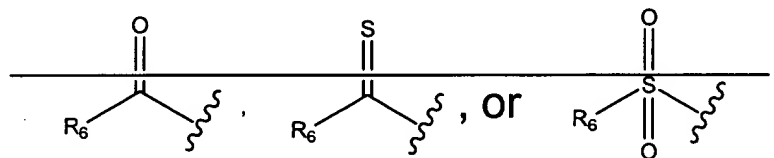
A represents a 4-8 membered heterocycle including a N and a C α carbon;

Z represents C or N;

W represents $-\text{CH}=\text{NR}_5$;



R₁ represents a C-terminally linked amino acid residue or amino acid analog, a C-terminally linked peptide or peptide analog, or an amino-protecting group,



R₂ is absent or represents one or more substitutions to the ring A, each of which can

independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-OH}$, $-(\text{CH}_2)_m\text{-O-lower alkyl}$, $-(\text{CH}_2)_m\text{-O-lower alkenyl}$, $-(\text{CH}_2)_n\text{-O}-(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-SH}$, $-(\text{CH}_2)_m\text{-S-lower alkyl}$, $-(\text{CH}_2)_m\text{-S-lower alkenyl}$, or $-(\text{CH}_2)_n\text{-S}-(\text{CH}_2)_m\text{-R}_7$;

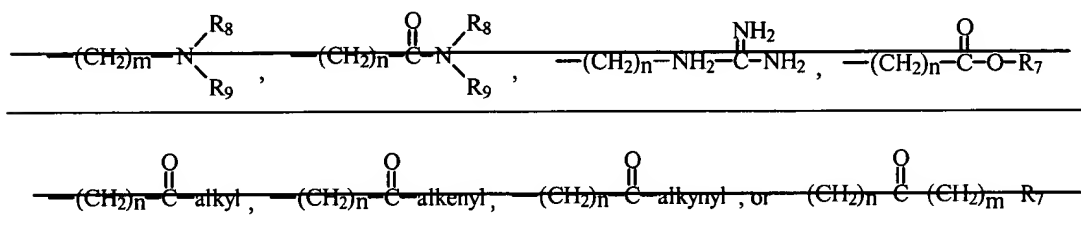
if Z is N, R₃ represents a hydrogen;

if Z is C, R₃ represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-OH}$, $-(\text{CH}_2)_m\text{-O-lower alkyl}$,

$-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl,
 $-(CH_2)_m-S$ -lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $C(X_1)(X_2)X_3$, $(CH_2)_m-R_7$, $(CH_2)_n-OH$, $(CH_2)_n-O$ alkyl, $(CH_2)_n-O$ alkenyl, $(CH_2)_n-O$ alkynyl, $(CH_2)_n-O-(CH_2)_m-R_7$, $(CH_2)_n-SH$, $(CH_2)_n-S$ alkyl, $(CH_2)_n-S$ alkenyl, $(CH_2)_n-S$ alkynyl, $(CH_2)_n-S-(CH_2)_m-R_7$, $C(O)C(O)NH_2$, or $C(O)C(O)OR'_7$;

R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $(CH_2)_m-R_7$, $(CH_2)_m-OH$, $(CH_2)_m-O$ alkyl, $(CH_2)_m-O$ alkenyl, $(CH_2)_m-O$ alkynyl, $(CH_2)_m-O-(CH_2)_m-R_7$, $(CH_2)_m-SH$, $(CH_2)_m-S$ alkyl, $(CH_2)_m-S$ alkenyl, $(CH_2)_m-S$ alkynyl, $(CH_2)_m-S-(CH_2)_m-R_7$;



R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $(CH_2)_m-R_7$, $C(=O)$ alkyl, $C(=O)$ alkenyl, $C(=O)$ alkynyl, or $C(=O)-(CH_2)_m-R_7$;

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3 , SH, NH_2 , NO_2 or OR'_7 ;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7 , or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y_1 and Y_2 can independently or together be OH or an alkoxyl, or taken together Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

~~X_1 represents a halogen;~~

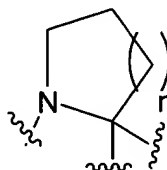
~~X_2 and X_3 each represent a hydrogen or a halogen;~~

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

55. (Canceled)

56. (Previously Presented) The method of claim 54, wherein the ring A is represented by the formula

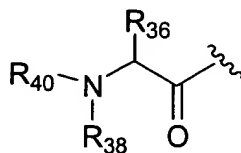


wherein,

n is an integer of 1 or 2.

57. (Canceled)

58. (Previously Presented) The method of claim 54, wherein R_1 represents



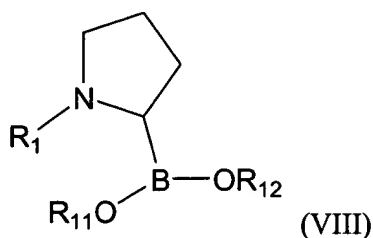
R_{36} represents a small hydrophobic group and R_{38} is hydrogen, or, R_{36} and R_{38} together form a 4-7 membered heterocycle including the N and the $C\alpha$ carbon, as defined for A above; and R_{40} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

59. (Previously Presented) The method of claim 54, wherein R_2 is absent, or represents a small hydrophobic group.

60. (Previously Presented) The method of claim 54, wherein R_3 is a hydrogen, or a small hydrophobic group.

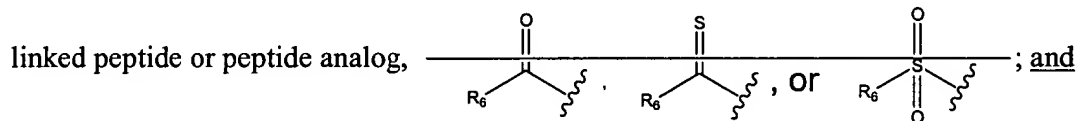
61-62. (Canceled)

63. (Currently Amended) The method of claim 54, wherein the inhibitor is represented by the general Formula (VIII):

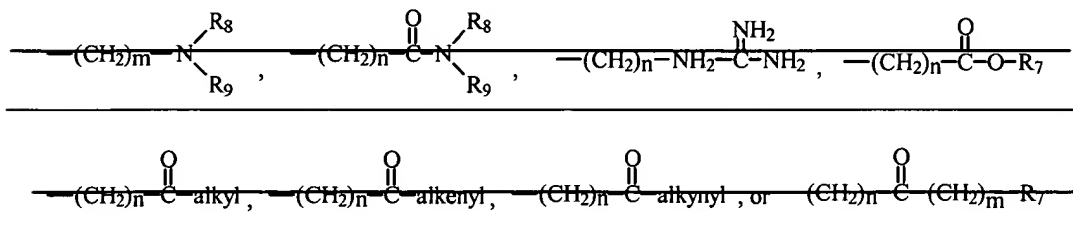


wherein,

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally



~~R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $(\text{CH}_2)_m\text{---R}_7$, $(\text{CH}_2)_m\text{---OH}$, $(\text{CH}_2)_m\text{---O---alkyl}$, $(\text{CH}_2)_m\text{---O---alkenyl}$, $(\text{CH}_2)_m\text{---O---alkynyl}$, $(\text{CH}_2)_m\text{---O---}$, $(\text{CH}_2)_m\text{---R}_7$, $(\text{CH}_2)_m\text{---SH}$, $(\text{CH}_2)_m\text{---S---alkyl}$, $(\text{CH}_2)_m\text{---S---alkenyl}$, $(\text{CH}_2)_m\text{---S---alkynyl}$, $(\text{CH}_2)_m\text{---S---}(\text{CH}_2)_m\text{---R}_7$,~~



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

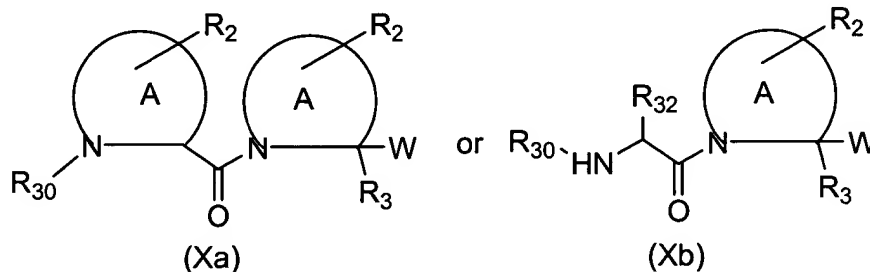
~~R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $(\text{CH}_2)_m\text{---R}_7$, C(=O)---alkyl , C(=O)---alkenyl , C(=O)---alkynyl , or $\text{C(=O)---}(\text{CH}_2)_m\text{---R}_7$,~~

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{11} and R_{12} each independently represent hydrogen, an alkyl, or a pharmaceutically acceptable salt, or R_{11} and R_{12} taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;
 ~~m is zero or an integer in the range of 1 to 8; and~~
 ~~n is an integer in the range of 1 to 8.~~

64-65. (Canceled)

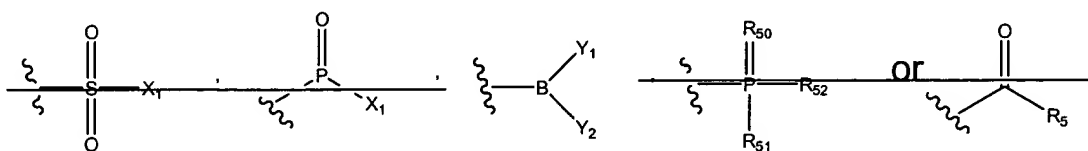
66. (Currently Amended) The method of claim 54, wherein the inhibitor is represented by the general Formula Xa or Xb:



wherein,

A represents a 4- to 8-membered heterocycle including a N and a C α carbon;

W represents $-\text{CH}=\text{NR}_5$,



R_2 is absent or represents one or more substitutions to the ring A, each of which can

independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-OH}$, $-(\text{CH}_2)_m\text{-O-lower alkyl}$, $-(\text{CH}_2)_m\text{-O-lower alkenyl}$, $-(\text{CH}_2)_n\text{-O}-(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-SH}$, $-(\text{CH}_2)_m\text{-S-lower alkyl}$, $-(\text{CH}_2)_m\text{-S-lower alkenyl}$, or $-(\text{CH}_2)_n\text{-S}-(\text{CH}_2)_m\text{-R}_7$;

R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a

sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

~~R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $C(X_1)(X_2)X_3$, $(CH_2)_m-R_7$, $(CH_2)_n-OH$, $(CH_2)_n-O$ alkyl, $(CH_2)_n-O$ alkenyl, $(CH_2)_n-O$ alkynyl, $(CH_2)_n-O-(CH_2)_m-R_7$, $(CH_2)_n-SH$, $(CH_2)_n-S$ alkyl, $(CH_2)_n-S$ alkenyl, $(CH_2)_n-S$ alkynyl, $(CH_2)_n-S-(CH_2)_m-R_7$, $C(O)C(O)NH_2$, or $C(O)C(O)OR'_7$;~~

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

~~R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;~~

R_{32} is a small hydrophobic group;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group;

~~R_{50} represents O or S;~~

~~R_{51} represents N_3 , SH, NH_2 , NO_2 or OR'_7 ;~~

~~R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7 , or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;~~

Y_1 and Y_2 can independently or together be OH or an alkoxy, or taken together Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

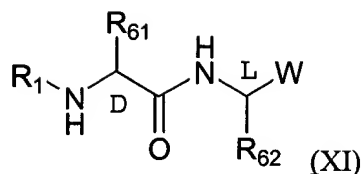
~~X_1 represents a halogen;~~

~~X_2 and X_3 each represent a hydrogen or a halogen;~~

m is zero or an integer in the range of 1 to 8; and

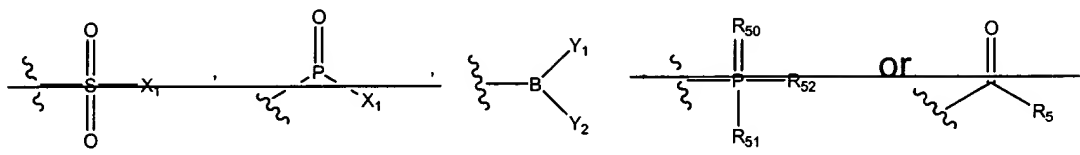
n is an integer in the range of 1 to 8.

67. (Currently Amended) The method of any one of claims 38, 39, or 40, wherein the inhibitor is represented by the general Formula XI:

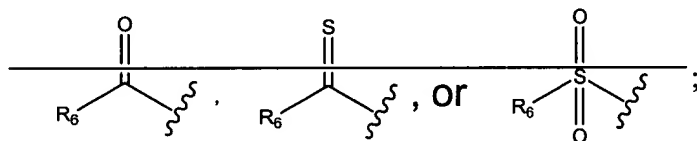


wherein,

W represents a functional group which reacts with an active site residue of the targeted protease selected from ~~CN~~, ~~CH=NR₅~~;



R₁ represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, ~~or~~



~~R₃ represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amide, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, (CH₂)_m-R₇, (CH₂)_m-OH, (CH₂)_m-O lower alkyl, (CH₂)_m-O lower alkenyl, (CH₂)_n-O (CH₂)_m-R₇, (CH₂)_m-SH, (CH₂)_m-S lower alkyl, (CH₂)_m-S lower alkenyl, or (CH₂)_n-S (CH₂)_m-R₇;~~

~~R₅ represents H, an alkyl, an alkenyl, an alkynyl, C(X₁)(X₂)X₃, (CH₂)_m-R₇, (CH₂)_n-OH, (CH₂)_n-O alkyl, (CH₂)_n-O alkenyl, (CH₂)_n-O alkynyl, (CH₂)_n-O (CH₂)_m-R₇, (CH₂)_n-SH, (CH₂)_n-S alkyl, (CH₂)_n-S alkenyl, (CH₂)_n-S alkynyl, (CH₂)_n-S (CH₂)_m-R₇, C(O)C(O)NH₂, or C(O)C(O)OR₇;~~

~~R₆ represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, (CH₂)_m-R₇, (CH₂)_m-OH, (CH₂)_m-O alkyl, (CH₂)_m-O alkenyl, (CH₂)_m-O alkynyl, (CH₂)_m-O (CH₂)_m-R₇, (CH₂)_m-SH, (CH₂)_m-S alkyl, (CH₂)_m-S alkenyl, (CH₂)_m-S alkynyl, or (CH₂)_m-S (CH₂)_m-R₇;~~

~~R₇ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;~~

~~R'₇ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;~~

R₆₁ and R₆₂, independently, represent small hydrophobic groups; and

Y₁ and Y₂ can independently or together be OH or an alkoxyl, or taken together Y₁ and Y₂ are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

~~R₅₀ represents O or S;~~

~~R₅₁ represents N₃, SH, NH₂, NO₂ or OR'₇;~~

~~R₅₂ represents hydrogen, a lower alkyl, an amine, OR'₇, or a pharmaceutically acceptable salt, or R₅₁ and R₅₂ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;~~

~~X₁ represents a halogen;~~

~~X₂ and X₃, independently for each occurrence, represent a hydrogen or a halogen;~~

~~m is zero or an integer in the range of 1 to 8; and~~

~~n is an integer in the range of 1 to 8.~~

68. (Previously Presented) The method of any one of claims 38-40, wherein the total dosage is less than 2000 mg.